EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	("6623752").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2007/05/30 16:08
S1	1687	pergolide	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/30 15:40
S2	1607	S1 and (composition or preparat$)	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/27 16:05
S3	945	S2 and transderm$	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/27 16:06
S4	0	S3 and plymer	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/27 16:06
S5	667	S3 and polymer	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/27 16:07
S6	0	S4 and patch	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/27 16:06
S7	768	S3 and patch	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/27 16:07
S8	578	S3 and $patch	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/27 16:07
S9	962	pergolide and transderma$	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/27 16:11

EAST Search History

S10	69344	pergolide near "15" transderma$	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/27 16:11
S11	29	pergolide near15 transderma$	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/27 16:11
S12	2197	424/449.ccls.	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/30 15:40
S13	53	S12 and pergolid$	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/30 15:44
S14	53	S13 and (transderm$ or $patch or $plaster)	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/30 15:43
S15	53	S14 and py<"2003"	US-PGPUB; USPAT; USOCR; EPO; DERWENT	OR	ON	2007/05/30 15:43

16 ANSWER 1 OF 4 USPATFULL on STN

ACCESSION NUMBER:	2007:94338 USPATFULL <<LOGINID::20070529>>			
TITLE:	Transdermal preparations and method for relieving side effects in pergolide therapy			
INVENTOR(S):	Toshimitsu, Arata, Ibaraki, JAPAN Aida, Kazunosuke, Ibaraki, JAPAN Terahara, Takaaki, Ibaraki, JAPAN Higo, Naruhito, Ibaraki, JAPAN			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2007082037	A1	20070412	
APPLICATION INFO.:	US 2004-577746	A1	20041029	(10)
	WO 2004-JP16091		20041029	
			20060427	PCT 371 date
	NUMBER		DATE	
PRIORITY INFORMATION:	JP 2003-373601		20031031	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	LICATA & TYRRELL P.C., 66 E. MAIN STREET, MARLTON, NJ, 08053, US			
NUMBER OF CLAIMS:	12			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	3 Drawing Page(s)			
LINE COUNT:	752			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB It is intended to provide pergolide-containing transdermal preparations having reducreduced side effects and exerting sufficient therapeutic effects. Namely, a pergolide -containing transdermal preparation which is capable of achieving a plasma AUC ratio of pergolide or the like to at least one pergolide metabolite of 1:0.5 to 1:5; and/or transdermal preparation containing pergolide and/or a pharmaceutically acceptable salt thereof which is capable of achieving a ratio (A/B) of the maximum plasma level (A) of pergolide and/or a pharmaceutically acceptable salt thereof to the plasma level (B) thereof in the next administration of less than 2.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Transdermal preparations and method for relieving side effects in pergolide therapy

AB It is intended to provide pergolide-containing transdermal preparations having reducreduced side effects and exerting sufficient therapeutic effects. Namely, a pergolide -containing transdermal preparation which is capable of achieving a plasma AUC ratio of pergolide or the like to at least one pergolide metabolite of 1:0.5 to 1:5; and/or transdermal preparation containing pergolide and/or a pharmaceutically acceptable salt thereof which is capable of achieving a ratio (A/B) of the maximum plasma level (A) of pergolide and/or a pharmaceutically acceptable salt thereof to the plasma level (B) thereof in the next administration of less than 2.

SUMM The invention relates to a transdermal preparation which contains pergolide known as an anti-parkinsonism agent and/or a parmaceutically acceptable salt thereof (hereinafter described as pergolide or the like), is remarkably excellent in a skin permeability and low in skin irritation. More particularly, the invention relates to a transdermal pergolide preparation for a Parkinson's disease therapy, in which side effects are reduced by not only reducing a plasma level change of pergolide itself but suppressing formation of a metabolite of pergolide or the like (hereinafter described as a pergolide metabolite),

and a method of reducing side effects in a pergolide therapy.

SUMM . . . a long term administration, so that coadministration with a drug which is different in the action mechanism is carried out. Pergolide mesylate is one of dopamine agonists, and is widely used in a clinical treatment because its coadministration with levodopa not only. . .

SUMM However, the pergolide mesylate preparation, which can be used at present, is a tablet, and can not avoid metabolism/degradation in the liver, whereby the. . . since generally in a parkinsonism patient, a gastric function is lowered, there is such a problem that the bioavailability of pergolide by oral administration does not easily become constant. In particular, in order to avoid side effects accompanied by an abrupt rise of a plasma level of pergolide or the like and/or a metabolite thereof which results from change of the above bioavailability and effect of metabolism, in case of orally administering pergolide mesylate it gradual increase of one day dose is necessary for carrying out administration. Namely, 50 μg/day is administered till the. . . 1). In order to dissolve the above tedious dose-setting and instability of the effect accompanying this, in recent years several transdermal preparations containing pergolide or the like as a preparation which substitutes for an oral preparation have been proposed.

SUMM For example, in patent document 1 a composition for a transdermal administration by combination of a pharmaceutically acceptable salt of pergolide with a permeation enhancer is proposed. In addition, as a device to increase a skin permeability, in patent document 2 a matrix composition containing a layered pergolide and in patent document 3 a multiple layer transdermal preparation containing water are disclosed. Further, in patent documents 4 and 5, in a plaster of pergolide a method to strengthen the action by blend of an additional pharmaceutical ingredient and a pergolide-containing adhesive patch preparation which is low in skin irritation and excellent in physical stability are disclosed. In addition, in patent document 6 an adhesive patch to give an administration effect of a drug including pergolide in sufficiently high standard and stable state is disclosed.

SUMM However, in preparations described in any of the above documents, reducing of the above side effects due to pergolide or the like is disregarded from the objective, whereby said reducing is not described.

SUMM In patent document 7, a transdermal preparation, which increases skin permeability of a drug having ergoline skeleton like pergolide and also seeks reducing of side effects of the drug, is disclosed. However, the reducing method of side effects in said document mainly depends on a change of a dosage form from an oral form to a transdermal form.

SUMM . . . a preparation to reduce side effects of oxybutynin is disclosed. However, said document fails to provide any mention on a transdermal preparation containing pergolede as well as a therapeutic drug for Parkinson's disease: The document even fails to provide any specific information on reducing of side effects due to pergolide or the like.

SUMM Namely, although it has been tired to avoid influence due to metabolism by adopting a transdermal dosage-form and to sufficiently exert the drug effect of pergolide, a transdermal preparation to simultaneously suppress the side effects is yet to be obtained. Therefore, the development of a transdermal preparation which can be used in pergolide therapy is desired.

SUMM Thus, the object of the invention is to provide a transdermal preparation containing pergolide or the like which has not the above problems, that is, reduces side effects and exerts a sufficient therapeutic effect.

SUMM . . . in the prior arts described above, the inventors surprisingly found out that the above problems can be solved by suppressing pergolide metabolite formation or a peak appearance of the plasma level of a pergolide metabolite, and completed the invention as a result of further investigation.

SUMM Namely, the invention relates to a transdermal preparation containing pergolide or the like, which is capable of achieving a plasma AUC ratio of pergolide or the like to at least one pergolide metabolite of 1:0.5 to 1:5.

SUMM In addition, the invention relates to the above transdermal preparation, wherein the plasma AUC ratio of pergolide or the like to at least one pergolide metabolite of 1:0.5 to 1:3.5.

SUMM Further, the invention relates to the above transdermal preparation, wherein the plasma AUC ratio of pergolide or the like to at least one pergolide metabolite is 1:0.5 to 1:2.

SUMM In addition, the invention relates to the above transdermal preparation, wherein the pergolide metabolite is one or more kinds comprising pergolide sulfoxide, pergolide sulfone, despropyl pergolide or despropyl pergolide sulfoxide.

SUMM Further, the invention relates to the above transdermal preparation, wherein the pergolide metabolite is pergolide sulfoxide.

SUMM In addition, the invention relates to the above transdermal preparation, wherein the pharmaceutically acceptable salt is one or more kinds comprising hydrochloride, sulfate, mesylate, citrate, fumarate, tartarate, maleate or. . .

SUMM Further, the invention relates to the above transdermal preparation, wherein the pharmaceutically acceptable salt is mesylate.

SUMM In addition, the invention relates to the above transdermal preparation, wherein the ratio (A/B) of the maximum plasma level (A) of pergolide and/or the pharmaceutically acceptable salt thereof to the plasma level (B) thereof in the next administration and/or the ratio (A'/B') of the maximum plasma level (A') of pergolide sulfoxide to the plasma level (B') of pergolide sulfoxide in the next administration is less than 2.

SUMM Further, the invention relates to the above transdermal preparation, wherein (meth)acrylic acid copolymer is contained in an adhesive layer.

SUMM Furthermore, the invention relates to the above transdermal preparation, wherein the acrylic polymer except (meth) acrylic acid copolymer is further contained in an adhesive layer.

SUMM Further, the invention relates to the above transdermal preparation containing pergolide and/or the pharmaceutically acceptable salt thereof, wherein the ratio (A/B) of the maximum plasma level (A) of pergolide and/or the pharmaceutically acceptable salt thereof to the plasma level (B) thereof in the next administration and/or the ratio (A'/B') of the maximum plasma level (A') of pergolide sulfoxide to the plasma level (B') of pergolide sulfoxide in the next administration is less than 2.

SUMM Furthermore, the invention relates to anyone of the transdermal preparations described above, which is an adhesive patch.

SUMM In a transdermal preparation of the invention, by achieving a plasma AUC ratio of pergolide or the like to at least one pergolide metabolite of 1:0.5 to 1:5, the amount of a pergolide metabolite produced, which is causative for side effects, can be reduced, so that the side effects in pergolide therapy can remarkably be reduced.

SUMM On the other hand, in an oral administration of pergolide a peak of the plasma level of pergolide or the like and/or pergolide sulfoxide, which is a main metabolite thereof, in the first administration is significantly higher compared with that in the next. . . level in the next administration becomes difficult to be

achieved, which may cause insufficient therapeutic effects. Considering the information, the transdermal preparation of the invention suppresses the peak appearance of pergolide or the like and/or pergolide sulfoxide, thus reducing the side effects.

SUMM Namely, by using a pergolide-containing transdermal preparation of the invention, it is possible to have pergolide and/or a pharmaceutically acceptable salt thereof absorbed effectively in circulating blood via the skin, so that the preparation can simply be administered. In addition, by the pergolide-containing transdermal preparation of the invention, it is possible to reduce the side effects by suppressing a metabolite formation and/or of the peak appearance of pergolide or the like and/or pergolide sulfoxide, so that the pergolide-containing transdermal preparation of the invention is useful as a preparation for external use for a transdermal application of pergolide in a parkinsonism therapy.

SUMM The invention is a pergolide-containing transdermal preparation, which is capable of achieving a plasma AUC ratio of pergolide or the like to at least one pergolide metabolite of 1:0.5 to 1:5 and reducing side effects in a pergolide therapy. Therefore, by a transdermal preparation of the invention, side effects in the pergolide therapy can be reduced.

SUMM In addition, the transdermal preparations of the invention, which enable a plasma AUC ratio of pergolide or the like to at least one pergolide metabolite of 1:0.5 to 1:3.5, more preferably 1:0.5 to 1:2, enable reduction of the formation of at least one pergolide metabolite, so that more reamarkable reduction of the side effects in the pergolide therapy being achieved.

SUMM In addition, the transdermal preparations of the invention, in which at least one pergolide metabolite is one or more kinds comprising pergolide sulfoxide, pergolide sulfone, despropyl pergolide or despropyl pergolide sulfoxide, and is preferably pergolide sulfoxide, can suppress a pergolide metabolite formation which is considered to be a main factor of side effects in the pergolide therapy, so that more remarkable reduction of the side effects being achieved.

SUMM In addition, the transdermal preparations of the invention, in which a pharmaceutically acceptable salt is one or more kinds comprising hydrochloride, sulfate, mesylate, citrate, fumarate, tartarate, maleate or acetate, can widen choices of pergolide or the like used in the pergolide therapy because wider range of salts of pergolide can be used. Among the above pharmaceutically acceptable salts mesylate is particularly preferable.

SUMM Further, the transdermal preparations of the invention those, in which the ratio (A/B) of the maximum plasma level (A) of pergolide and/or a pharmaceutically acceptable salt thereof to the plasma level (B) thereof in the next administration and/or the ratio (A'/B') of the maximum plasma level (A') of pergolide sulfoxide to the plasma level (B') of pergolide sulfoxide in the next administration is less than 2, side effects due to pergolide or the like per se can be reduced and side effects due to pergolide sulfoxide can more surely be reduced, so that more effective pergolide therapy can be carried out.

SUMM Furthermore, the transdermal preparations of the invention, in which (meth)acrylic acid copolymer is contained in an adhesive layer enables easier control of a plasma AUC ratio of pergolide or the like to at least one pergolide metabolite, more effective control of side effects in the pergolide therapy being achieved. Those further having the acrylic polymer except (meth) acrylic acid copolymer in the adhesive layer can enable more effective control of the side effects.

SUMM Further, by a transdermal preparation of the invention

containing pergolide and/or a pharmaceutically acceptable salt thereof, wherein the ratio (A/B) of the maximum plasma level (A) of pergolide and/or a pharmaceutically acceptable salt thereof to the plasma level (B) thereof in the next administration and/or the ratio (A'/B') of the maximum plasma level (A') of pergolide sulfoxide to the plasma level (B') of pergolide sulfoxide in the next administration is less than 2, side effects due to pergolide or the like themselves can be reduced and/or side effects due to pergolide sulfoxide can exactly be reduced, and therefore, the pergolide therapy can be carried out effectively.

SUMM In addition, the transdermal preparations of the invention, which are adhesive patches enable extremely simple and clean administration of pergolide or the like.

SUMM In the invention, "pergolide therapy" means a preventive or therapeutic treatments using pergolide or the like.

SUMM One of the transdermal preparation of the invention is characterized in that as described above a plasma AUC of pergolide or the like to at least one pergolide metabolite is made 1:0.5 to 1:5. In view of reducing side effects due to the metabolite, the plasma AUC is. . .

SUMM In addition, another transdermal preparation of the invention is, with regard to the change of a drug plasma level in a repetitive administeration, a ratio (A/B) of the maximum plasma level (A) of pergolide to the plasma level (B) in the next administration and/or a ratio (A'/B') of the maximum plasma level (A') of pergolide sulfoxide to the plasma level (B') in the next administration have for the first time successfully been less than 2. In said transdermal preparation of the invention, in view of reducing side effects due to pergolide itself, (A/B) and/or (A'/B') are less than 2, preferably less than 1.5.

SUMM Further, a dosage form of the transdermal preparation of the invention is not limited as long as pergolide or the like are transdermally absorbed, so that those such as an ointment or a cream are included, an adhesive patch being preferable in view of simplicity and cleanliness in administration. Furthermore, in the case of the adhesive patch, a non-aqueous transdermal preparation is particularly preferable since pergolide and/or a pharmaceutically acceptable salt thereof being contained in a non-aqueous adhesive layer is provided with extremely favorable skin permeability with low skin irritation, in the transdermal preparation.

SUMM In the following, the transdermal preparation of the invention is illustrated in more detail.

SUMM The invention is a pergolide-containing transdermal preparation. Although a dosage form of the transdermal preparation of the invention is not particularly limited, the form of an adhesive patch is, for example, as shown in FIG. 1. In the following, the composition and form of the adhesive layer in the transdermal preparation of the invention are explained in detail.

SUMM A pharmacologically active ingredient in the transdermal preparation of the invention is pergolide and/or a pharmaceutically acceptable salt thereof: Pergolide or the like. The pharmaceutically acceptable salt is not particularly limited, it being possible said salt is an inorganic salt or an organic salt, while pergolide mesylate, which is a representative salt, is particularly preferable.

SUMM As for the transdermal preparation of the invention, pergolide or the like are preferably blended in an amount of 0.5-50 mass %. It becomes easy to obtain a sufficient drug permeation amount as a transdermal preparation by not less than 0.5 mass %, and it becomes possible to keep more preferably a physical property of. . .

SUMM Further, at least one pergolide metabolite is preferably one or more kinds comprising pergolide sulfoxide, pergolide sulfone, despropyl pergolide or despropyl pergolide sulfoxide, in particular preferably pergolide sulfoxide.

SUMM In a case that the dosage form of the invention is an adhesive patch, as a base for the adhesive layer, an acrylic polymer and/or a rubber polymer are preferably used.

SUMM As the acrylic polymer there is no particular restriction as long as it is copolymer containing at least one of (meth)acrylic acid derivatives represented by 2-ethylhexyl acrylate, methyl acrylate, butyl acrylate, hydroxyethyl acrylate, 2-ethylhexyl (meth)acrylate and the like. Examples thereof are as. . . liquid; DURO-TAK acryl adhesive series (manufactured by National Starch & Chemical), Eudragit series (Higuchi Shokai Co., Ltd.) and the like. (Meth)acrylic acid copolymer such as the above Eudragit series is preferable because of more effective reducing side effects. Those further containing in addition to (meth) acrylic acid copolymer further acrylic polymer are more preferable.

SUMM Those further containing acrylic polymer in addition to (meth)acrylic acid copolymer is preferable.

SUMM In the case of the adhesive force is not sufficient with the adhesive patch according to the invention, a tackifying resin is desirably contained in the adhesive layerUsable tackifying resins include rosin derivatives (e.g.. . .

SUMM Considering a sufficient adhesive force as an adhesive patch and irritation to the skin upon releasing, the blending amount of such a tackifying resin based on the total composition. . .

SUMM An absorption enhancer may be contained in the adhesive layer for an adhesive patch according to the invention. As a usable absorption enhancer, any compound which shows an absorption enhancing effect maybe used. Examples. . .

SUMM . . . it is desired to have an organic acid contained in the adhesive layer in the case that the form of pergolide is a pharmaceutically acceptable acid-addition salt. As organic acids used include aliphatic (mono-, di-, tri-)carboxylic acids (e.g. acetic acid, propionic. . .

SUMM The backing layer for an adhesive patch according to the invention is not particularly limited as long as it is appropriate for supporting the adhesive layer, although. . .

SUMM . . . (Eudragit EPO) 10.0%

Alicyclic saturated hydrocarbon resin (ARKON P 100)	35.0%
Liquid paraffin	15.0%
Acetic acid	6.0%
Sodium acetate	2.0%
Pergolide mesylate	9.0%
Sorbitan monolaurate	2.0%
Isostearyl alcohol	3.0%
Total amount	100.0%

SUMM Pergolide mesylate, acetic acid, sodium acetate, sorbitan monolaurate, isosteryl alchol and liquid paraffin were beforehand put in a mortar, and mixed thoroughly,. . . on a release liner, solvent was removed by drying, followed by affixing to a PET film backing to give the transdermal preparation of the invention.

SUMM . . . of a single administration of the preparation obtained in Example 1 to healthy adults (n=8) and the pharmacokinetic parameter of pergolide sulfoxide, main metabolite, are shown in Table 2 and Table 3 respectively. In addition, the pharmacokinetic parameter of Permax which is an oral preparation of pergolide is also shown simultaneously for comparison.

SUMM Based on Tables 2 and 3, the AUC ratios of pergolide mesylate to its main metabolite, pergolide sulfoxide,

in Permax tablet and Example 1 (administration amounts, 1.35 mg, 2.7 mg, 5.4 mg and 10.8 mg; corresponding to. . . cm.sup.2, 4 cm.sup.2, 8 cm.sup.2 and 16 cm.sup.2 respectively) became 1:14.1, 1:1.03, 1:0.91, 1:0.83 and 1:0.89 respectively. Namely, in the transdermal preparation of the invention, the AUC ratios of pergolide mesylate to its metabolite were 1/17 to 1/14 compared with Permax tablet, being extremely small. Further, the side effects in this case (sleepiness, vomiting and headache) were significantly small in case of administering the transdermal preparation of the invention compared with administering Permax tablet (Table 4). In particular, in the administration parts of 2.7 mg,. . .

SUMM Among each drug preparation used in (5), the plasma levels of pergolide and pergolide sulfoxide in case of repetitively administering 8 cm.sup.2 preparation and 16 cm.sup.2 preparation related to the example of the invention and Permax tablet of oral preparation at 24 hr interval were obtained by the following simulation. Further, as to pergolide sulfoxide, the simulation was carried out only for 16 cm.sup.2 preparation.

SUMM In the transdermal preparation of the invention, the plasma level measured in a single administration was successively added every 24 hr, and a. . .

SUMM As to Permax tablet, the simulation was carried out in a similar manner to the above transdermal preparation of the invention in accordance to a standard administration method.

SUMM As the results, the ratio (A/B) of the maximum plasma level (A) of pergolide in the first administration to the plasma level (B) at the time of the second administration and the ratio (A'/B') of the maximum plasma level (A') of pergolide sulfoxide in the first administration to the plasma level (B') at the time of the second administration became 1.0 parallel. . .

SUMM In the mean time, in Permax the maximum plasma level (A) of pergolide after the first administration was 6.70 pg/ml, and the plasma level (B) at the time of the second administration, that. . .

SUMM Based on the above results, it was confirmed that the pergolide -containing transdermal preparation of the invention was excellent in a drug permeation rate and was sufficiently good for a practical use concerning a skin irritation and a physical property of the preparation. In addition, in the transdermal preparation of the invention it also became apparent that side effects accompanied with a metabolite were remarkably reduced because the. . .

SUMM Further, in the transdermal preparation of the invention it was confirmed that side effects of pergolide itself and its main metabolite could remarkably be reduced because the ratio (A/B) of the maximum plasma level (A) of pergolide in the first administration to the plasma level (B) at the time of the second administration and the ratio (A'/B') of the maximum plasma level (A') of pergolide sulfoxide in the first administration to the plasma level (B') at the time of the second administration can be led. . .

SUMM By using a pergolide-containing transdermal preparation of the invention, it is possible to let pergolide and/or a pharmaceutically acceptable salt thereof be absorbed effectively in circulating blood via the skin, and the preparation can simply be administered. In addition, by the pergolide -containing transdermal preparation of the invention, it is possible to reduce the side effects by suppressing the formation of at least one metabolite. Further, the pergolide-containing transdermal preparation of the invention has favorable stickiness to the skin and is useful as a preparation for external use which makes a trasdermal application of pergolide in a parkinsonism therapy an object.

SUMM Therefore, the pergolide-containing transdermal preparation of the invention greatly contributes to the development of pharmaceutical industry as well as related industries.

DRWD FIG. 1 shows one embodiment of a pergolide-containing

transdermal preparation of the invention.

DRWD . . . 2 shows a age change of the plasma level of unchanged substance in case of a single administration of a pergolide -containing transdermal preparation of the invention.

DRWD FIG. 3 shows a age change of the plasma level of the main metabolite (pergolide sulfoxide) in case of a single administration of a pergolide-containing transdermal preparation of the invention.

DRWD FIG. 4 shows a simulation result of the age change of the plasma level of pergolide in case of a repetitive administration of a pergolide-containing transdermal preparation of the invention.

DRWD FIG. 5 shows a simulation result of the age change of the plasma level of pergolide sulfoxide in case of a repetitive administration of a pergolide-containing transdermal preparation of the invention.

CLM What is claimed is:

1. A transdermal preparation containing pergolide and/or a pharmaceutically acceptable salt thereof, wherein said preparation is capable of achieving a plasma AUC ratio of pergolide or the pharmaceutically acceptable salt thereof to at least one metabolite thereof of 1:0.5 to 1:5.

2. The transdermal preparation according to claim 1, wherein the plasma AUC ratio of pergolide and/or a pharmaceutically acceptable salt thereof to at least one metabolite thereof is 1:0.5 to 1:3.5.

3. The transdermal preparation according to claim 2, wherein the plasma AUC ratio of pergolide and/or a pharmaceutically acceptable salt thereof to at least one metabolite thereof is 1:0.5 to 1:2.

4. The transdermal preparation according to claim 1, wherein the metabolite is one or more kinds comprising pergolide sulfoxide, pergolide sulfone, despropyl pergolide or despropyl pergolide sulfoxide.

5. The transdermal preparation according to claim 4, wherein the metabolite is pergolide sulfoxide.

6. The transdermal preparation according to claim 1, wherein the pharmaceutically acceptable salt is one or more kinds comprising hydrochloride, sulfate, mesylate, citrate,. . .

7. The transdermal preparation according to claim 6, wherein the pharmaceutically acceptable salt is mesylate.

8. The transdermal preparation according to claim 1, wherein the ratio (A/B) of the maximum plasma level (A) of pergolide and/or the pharmaceutically acceptable salt thereof to the plasma level (B) thereof in the next administration and/or the ratio (A'/B') of the maximum plasma level (A') of pergolide sulfoxide to the plasma level (B') of pergolide sulfoxide in the next administration is less than 2.

9. The transdermal preparation according to claim 1, wherein (meth)acrylic acid copolymer is contained in an adhesive layer.

10. The transdermal preparation according to claim 9, wherein the acrylic polymer except (meth)acrylic acid copolymer is further contained in an adhesive layer.

11. A transdermal preparation containing pergolide

and/or the pharmaceutically acceptable salt thereof, wherein the ratio (A/B) of the maximum plasma level (A) of pergolide and/or the pharmaceutically acceptable salt thereof to the plasma level (B) thereof in the next administration and/or the ratio (A'/B') of the maximum plasma level (A') of pergolide sulfoxide to the plasma level (B') of pergolide sulfoxide in the next administration is less than 2.

12. The transdermal preparation according to claim 1, wherein said preparation is an adhesive patch.

L16 ANSWER 2 OF 4 USPATFULL on STN

ACCESSION NUMBER:	2007:4427 USPATFULL <<LOGINID::20070529>>
TITLE:	Dosage forms for movement disorder treatment
INVENTOR(S):	Nangia, Avinash, Sharon, MA, UNITED STATES Jacob, Jules, Taunton, MA, UNITED STATES Yeh, James, Foxboro, MA, UNITED STATES Moslemy, Peyman, Providence, RI, UNITED STATES Verma, Daya D., Needham, MA, UNITED STATES Haswani, Dinesh K., Plainville, MA, UNITED STATES Shaked, Ze'ev, San Antonio, TX, UNITED STATES
PATENT ASSIGNEE(S):	Spherics, Inc., Mansfield, MA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2007003621	A1	20070104	
APPLICATION INFO.:	US 2006-474524	A1	20060623	(11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2005-693602P	20050623 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	FISH & NEAVE IP GROUP, ROPES & GRAY LLP, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624, US
NUMBER OF CLAIMS:	21
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	97 Drawing Page(s)
LINE COUNT:	10125

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to the improvement in the treatment of certain neural disorders/diseases, such as Parkinson's disease and other motor disorders. One aspect of the invention relates to drug compositions and dosage forms comprising said drug composition. Another aspect of the invention relates to methods of manufacturing the drug compositions and dosage forms. Another aspect of the invention relates to methods of treatment, comprising administering the drug composition and dosage form to an individual.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . (ARTANE®), benztropine (COGENTIN®), ethoproprazine (PARSITAN®), or procyclidine (KEMADRIN®); a dopamine agonist, such as apomorphine, bromocriptine (PARLODEL®), cabergoline (DOSTINEX®), lisuride (DOPERGINE®), pergolide (PERMAX®, pramipexole (MIRAPEX®), or ropinirole (REQUIP®); a MAO-B (monoamine oxidase B) inhibitor, such as selegiline or deprenyl (ATAPRYL®, CARBEX®, ELDEPRYL®);. . .

SUMM Another aspect of the invention provides a pharmaceutical preparation comprising the subject pharmaceutical composition, provided in the form of a transdermal patch and formulated for sustained release of the pharmaceutical composition in order to administer an amount sufficient to treat a patient. . . release over at least about

6, 7, 8, 9, 10, 12, 14, 16, 18, 20 or more hours when the patch is applied to the patient.

DRWD . . . inner trilayer core is coated with a semi-permeable coating 54a, which is then coated over by a bioadhesive layer or patch (hatched lines) 54b. The therapeutic compositions are successively released through an orifice 56 close to the IR composition (proximal end). . . .

DRWD . . . a schematic drawing (not to scale) illustrating a cross-sectional view of one design of the subject delivery device--a bioadhesive buccal patch or buccal tablet attaching to a mucosa of the mouth 1201. The immediate-release composition layer 1202 covers one sub-portion of. . . composition CR2 1204 (or the second IR release portion). The whole device may be formulated as a multilaminate bioadhesive buccal patch or tablet attaching to a mucosa area of the mouth. Either or both CR layers may have their own bioadhesive layer or patch (not shown).

DETD . . . more reproducible and consistent plasma level of levodopa, a drug with a narrow absorption window. In certain embodiments, the bioadhesive layer/patch is used in conjunction with the substantially zero-order release composition.

DETD By "transdermal patch" is meant a system capable of delivery of a drug to a patient via the skin, or any suitable external. . .

DETD Certain embodiments of the invention provide a pharmaceutical preparation/dosage formulation provided in the form of a transdermal patch and formulated for sustained release formulation, in a therapeutically effective amount sufficient to treat a movement disorder (e.g., Parkinson's disease and related movement disorders) in a patient, wherein the dosage formulation, when administered (provided as a patch) to the patient, provides a substantially sustained dose over at least about 2 hours, 4 hours, 6 hours, 8, hours,. . .

DETD In either oral or patch form, the above-described dosage preparation can be one wherein the pharmaceutical composition is formulated in a multiplicity of (sub-)portions or. . .

DETD . . . (ARTANE®), benztropine (COGENTIN®), ethoproprazine (PARSITAN®), or procyclidine (KEMADRIN®); a dopamine agonist, such as apomorphine, bromocriptine (PARLODEL®), cabergoline (DOSTINEX®), lisuride (DOPERGINE®), pergolide (PERMAX®), pramipexole (MIRAPEX®), or ropinirole (REQUIP®); a MAO-B (monoamine oxidase B) inhibitor, such as selegiline or deprenyl (ATAPRYL®, CARBEX®, ELDEPRYL®);. . .

DETD . . . bromocriptine, budipine, cabergoline, clozapine, deprenyl, dextromethorphan, dihydroergokryptine, dihydrolipoic acid, eliprodil, eptastigmine, ergoline, formoterol, galanthamine, lazabemide, lysuride, mazindol, memantine, mofegiline, orphenadrine, pergolide, pirbuterol, pramipexole, propentofylline, procyclidine, rasagiline, remacemide, riluzole, rimantadine, ropinirole, salmeterol, selegiline, spheramine, terguride, and trihexyphenidyl.

DETD . . . CR®) or Levodopa-benserazide (PROLOPA®, MADOPAR®, MADOPAR HBS®); a sedative, such as clonazepam (RIVOTRIL®); a dopamine agonists, such as bromocriptine (PARLODEL®), pergolide (PERMAX®), pramipexole (MIRAPEX®), or ropinirole (REQUIP®); a narcotic agent, such as codeine (TYLENOL # 3®); or a GABAergic agent, such. . .

DETD . . . by their specific compositions (for example, the ratio of carbidopa/levodopa in the Parkinson disease therapeutic composition). A bioadhesive layer or patch (hatched lines) is shown to be on the outside wall of the shell encompassing the therapeutic compositions, which are successively. . .

DETD FIG. 12 shows yet another embodiment depicting a multilaminate bioadhesive buccal patch or tablet. The dosage form attaches to the mucosa surface (preferably through a bioadhesive layer attached to the CR2 layer,. . .

DETD In yet other embodiments, the subject pharmaceutical compositions are delivered by way of a transdermal patch, a buccal patch, or a buccal tablet. A patch is generally a flat hollow device with a permeable membrane on one side and also some form of adhesive to maintain the patch in place on the patient's skin, with the membrane in contact with the skin so that the medication can diffuse out of the patch reservoir and into and through the skin. The outer side of the patch is formed of an impermeable layer of material, and the membrane side and the outer side are joined around the perimeter of the patch, forming a reservoir for the medication and carrier between the two layers.

DETD Patch technology is based on the ability to hold an active ingredient in constant contact with the epidermis. Over substantial periods of time, drug molecules, held in such a state, will eventually find their way into the bloodstream. Thus, patch technology relies on the ability of the human body to pick up drug molecules through the skin. Transdermal drug delivery using patch technology has recently been applied for delivery of nicotine, in an effort to assist smokers in quitting, the delivery of. . . nitroglycerine to angina sufferers, the delivery of replacement hormones in post-menopausal women, etc. These conventional drug delivery systems comprise a patch with an active ingredient such as a drug incorporated therein, the patch also including an adhesive for attachment to the skin so as to place the active ingredient in close proximity to the skin. Exemplary patch technologies are available from Ciba-Geigy Corporation and Alza Corporation. Such transdermal delivery devices can be readily adapted for use with the subject pharmaceutical compositions.

DETD . . . and methyl laurate are disclosed in U.S. Pat. No. 4,973,468. A dual enhancer comprising glycerol monolaurate and ethanol for the transdermal delivery of drugs is shown in U.S. Pat. No. 4,820,720. U.S. Pat. No. 5,006,342 lists numerous enhancers for transdermal drug administration comprising fatty acid esters or fatty alcohol ethers of C2 to C4 alkanediols, where each fatty acid/alcohol portion. . .

DETD The patch preferably comprises a drug-impermeable backing layer. Suitable examples of drug-impermeable backing layers which may be used for transdermal or medicated patches include films or sheets of polyolefins, polyesters, polyurethanes, polyvinyl alcohols, polyvinyl chlorides, polyvinylidene chloride, polyamides, ethylene-vinyl acetate. . .

DETD In some embodiments, one can use non-biodegradable polymers, especially hydrophobic polymers. Examples of preferred non-biodegradable polymers include ethylene vinyl acetate, poly(meth)acrylic acid, copolymers of maleic anhydride with other unsaturated polymerizable monomers, poly(butadiene maleic anhydride), polyamides, copolymers and mixtures thereof, and dextran, cellulose. . .

L16 ANSWER 3 OF 4 USPATFULL on STN

ACCESSION NUMBER: 2006:79936 USPATFULL <<LOGINID::20070529>>

TITLE: Methods and compositions related to the modulation of intercellular junctions

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DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOLF GREENFIELD & SACKS, PC, FEDERAL RESERVE PLAZA, 600 ATLANTIC AVENUE, BOSTON, MA, 02210-2211, US
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Page(s)
LINE COUNT: 3765
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to compositions and methods for the modulation of the permeability of the epithelial cell barrier complex. In particular, the invention provides compositions and methods for using polysaccharides, preferably glycosaminoglycans, and agents that modify cell surface glycosaminoglycans, preferably glycosaminoglycan-degrading enzymes to modulate intercellular junctions. The compositions and methods provided can be used to facilitate the delivery of biologically active molecules.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . In some embodiments the intercellular junction disruption agents and/or biologically active agents provided are administered via an ocular, nasal, topical, transdermal, or rectal route. In one embodiment the agent is administered via a nasal route in order to facilitate the delivery. . . For topical administration, in some embodiments, the agent is in an ointment, lotion, spray, gel, cream, swab, wipe, bandage or patch. In another embodiment the agent is administered via a sublingual or gastrointestinal route to deliver it to systemic circulation. In. . .

SUMM . . . agent is administered via a route that is not oral and/or not gastrointestinal. In another embodiment the administration is not transdermal administration.

SUMM . . . biologically active agent are provided. In some embodiments the administration is carried out with a bandage, slow or controlled release patch, engineered or biodegradable scaffold, slow or controlled release polymer, tablet or capsule. In some embodiments the intercellular junction disruption agent. . .

SUMM . . . In one embodiment the form suitable for topical administration is an ointment, lotion, spray, gel, cream, swab, wipe, bandage or patch.

SUMM In still another embodiment the agent is a hormone therapy. In one embodiment the hormone therapy is Combipatch.RTM. (estradiol/norethindrone acetate), Androgel® (testosterone gel), Arimidex® (anastrozole), Casodex® (bicalutamide), Claripel.TM. (hydroquinone USP), Cytomel® (liothyrone sodium), Delatestryl® (testosterone enanthate), or Epiquine.TM.. . .

DETD . . . and exit across the membrane on the other side. Since non-invasive routes of drug delivery (which mainly includes oral, nasal, transdermal, ocular, rectal and other non-parenteral routes) are receiving increasing attention, transepithelial transport mechanisms are gaining more and more importance. Paracellular. . .

DETD . . . as a route of systemic drug administration because it has a number of advantages over more conventional routes of delivery. Transdermal delivery of drugs can be achieved by modulating the epithelial barrier function of the skin. Thus, epithelial permeability modulators like the intercellular junction disruption agents provided can effectively be used for transdermal delivery of drugs. Therefore, the compositions and methods provided can be used for the treatment of chronic wounds and subdermal. . .

DETD . . . Methocarbamol, Orphenadrine, Riluzole, Tizanidine);

Anti-Parkinsonism Agents (also movement disorder agents) (e.g., Amantadine, Benztropine, Biperiden, Bromocriptine, Carbidopa, Entacapone, Levodopa, Orphenadrine, Penicillamine, Pergolide, Pramipexole, Procyclidine, Ropinirole, Selegiline, Tolcapone, Trientine, Trihexyphenidyl); Antipsychotic Agents (e.g., Acetophenazine, Chlorpromazine, Chlorprothixene, Clozapine, Fluphenazine (& esters), Haloperidol (& esters),. . .

DETD . . . dose according to sound medical judgment. The mode of administration may be any medically acceptable mode including oral, ocular, topical, transdermal, rectal, nasal, subcutaneous, intravenous, etc. or via administration to a mucous membrane. In some embodiments the mode of administration is. . .

DETD . . . intraperitoneal, intrasternal injection or infusion techniques. Other modes of administration include oral, mucosal, rectal, vaginal, sublingual, intranasal, intratracheal, inhalation, ocular, transdermal, etc. In some embodiments the administration of the compositions does not occur via the pulmonary route.

DETD . . . are administered in aerosol form. In other embodiments the method of administration includes the use of a bandage, slow release patch, engineered or biodegradable scaffold, slow release polymer, tablet or capsule.

DETD . . . disruption agent is not administered intravenously and/or subcutaneously. In yet other embodiments the intercellular junction disruption agent is not administered transdermally.

DETD Examples of preferred non-biodegradable polymers include ethylene vinyl acetate, poly(meth) acrylic acid, polyamides, copolymers and mixtures thereof.

DETD . . . a monitor which can be placed on the surface of the skin, e.g., in the form of a ring or patch, and which can detect the level of circulating agents. One method for detection may be based on the presence of. . .

CLM What is claimed is:

. . . gel, and wherein the form suitable for topical administration is an ointment, lotion, spray, gel, cream, swab, wipe, bandage or patch, and wherein the form suitable for sublingual delivery is a sublingual tablet or oral gel.

L16 ANSWER 4 OF 4 USPATFULL on STN

ACCESSION NUMBER: 2006:53611 USPATFULL <<LOGINID::20070529>>

TITLE: 4-phenylbutyric acid controlled-release formulations for therapeutic use

INVENTOR(S): Truog, Peter, Chur, SWITZERLAND

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2006045912	A1	20060302	
APPLICATION INFO.:	US 2005-215576	A1	20050830	(11)

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FILE SEGMENT: APPLICATION

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NUMBER OF CLAIMS: 88

EXEMPLARY CLAIM: 1

LINE COUNT: 3279

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Controlled-release formulations and dosage forms containing 4-phenylbutyric acid sodium salt, or other pharmaceutically acceptable salts, esters or prodrugs, and a controlled release material for use in the treatment of diseases and disorders including neoplastic disorders

and neurodegenerative diseases The formulations provide extended release and extended half-life.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . The membrane can be non-porous, yet permeable to 4-PBA or it may be porous. Reservoir devices include oral, implantable or transdermal systems, for example.

SUMM . . . present invention may be non-degradable. Non-degradable polymers include, for example, polyacrylates, polymers of ethylene-vinyl acetates other acyl substituted cellulose acetates, poly(meth) acrylic acid, polyamides, polyethylene, polypropylene, non-degradable polyurethanes, polystyrene, polyvinyl chloride, polyvinylphenol, poly(vinyl imidazole), hlorosulphonate polyolefins, polyethylene oxide, blends, and copolymers thereof.

SUMM . . . cells and Useful for Oral or Mucosal Drug Delivery); U.S. Pat. No. 6,041,253 (Effect of Electric Field and Ultrasound for Transdermal Drug Delivery); U.S. Pat. No. 6,018,678 (Transdermal protein delivery or measurement using low-frequency sonophoresis); U.S. Pat. No. 6,007,845 Nanoparticles And Microparticles Of Non-Linear Hydrophilic-Hydrophobic Multiblock Copolymers; U.S. Pat. No. 6,004,534 Targeted Polymerized Liposomes For Improved Drug Delivery; U.S. Pat. No. 6,002,961 Transdermal Protein Delivery Using Low-Frequency Sonophoresis; U.S. Pat. No. 5,985,309 Preparation Of Particles For Inhalation; U.S. Pat. No. 5,947,921 Chemical And Physical Enhancers And Ultrasound For Transdermal Drug Delivery; U.S. Pat. No. 5,912,017 Multiwall Polymeric Microspheres; U.S. Pat. No. 5,911,223 Introduction Of Modifying Agents Into Skin By. . . Local Delivery Of Chemotherapeutic Agents For Treating Solid Tumors; U.S. Pat. No. 5,837,752 Semi-Interpenetrating Polymer Networks; U.S. Pat. No. 5,814,599 Transdermal Delivery Of Encapsulated Drugs; U.S. Pat. No. 5,804,178 Implantation Of Cell-Matrix Structure Adjacent Mesentery, Omentum Or Peritoneum Tissue; U.S. Pat.. . . membrane permeability; U.S. Pat. No. 4,779,806 Ultrasonically modulated polymeric devices for delivering compositions; U.S. Pat. No. 4,767,402 Ultrasound enhancement of transdermal drug delivery; U.S. Pat. No. 4,757,128 High molecular weight polyanhydride and preparation thereof; U.S. Pat. No. 4,657,543 Ultrasonically modulated polymeric. . .

SUMM Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches, optionally. . .

SUMM Formulations containing compounds of the invention may be administered through the skin by an appliance such as a transdermal patch. Patches can be made of a matrix such as polyacrylamide, polysiloxanes, or both and a semi-permeable membrane made from a suitable polymer to control the rate at which the material is delivered to the skin. Other suitable transdermal patch formulations and configurations are described in U.S. Pat. Nos. 5,296,222 and 5,271,940, as well as in Satas, D., et al,. . .

SUMM . . . of the invention are preferably administered by any appropriate administration route, for example, orally, parenterally, intravenously, intradermally, intramuscularly, subcutaneously, sublingually, transdermally, bronchially, pharyngolaryngeal, intranasally, topically such as by a cream or ointment, rectally, intraarticular, intracisternally, intrathecally, intravaginally, intraperitoneally, intraocularly, by inhalation,. . .

SUMM . . . movements, rigidity, expressionless face and stooped posture. Several drugs are available to increase dopaminergic function such as levodopa, carbidopa, bromocriptine, pergolide, or decrease cholinergic function such as benztropine, and amantadine. Selegiline is a new treatment designed to protect the remaining dopaminergic. . .